

### **REMARKS/ARGUMENTS**

Claims 1, 3, 4, and 12 are pending in this application after entry of this Amendment and have been amended to clarify the subject matter Applicants consider to be the invention. Claims 2, 5, 8-11 and 13 are canceled herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, with this amendment. Claims 6 and 7 were previously canceled. No new matter has been added.

A Declaration of inventor, Dr. Eckhard Guenther, is also attached hereto, which describes the unexpected synergistic effects of the claimed combinations for the treatment of breast cancer.

#### **A. Rejection of Claims under 35 U.S.C. § 103(a)**

**1.) Rejection of Claims 1-3 over Hilgard et al. Cancer Chemother. Pharmacol., (1993) 32:90-95 (“Hilgard”) in view of Calabresi et al., Goodman & Gilman’s, The Pharmacological Basis of Therapeutics, Ninth Edition (“Calabresi”).**

The Office action states that Hilgard teaches synergy when using miltefosine combined with a new cisplatin derivative in an in vivo mouse model. The Office action also states that a person of ordinary skill in the art would be motivated to employ Hilgard’s teaching because it had been known that both miltefosine and cisplatin derivatives have been employed in the treatment of carcinoma, and therefore combination of the drugs would have been obvious. The Office action states that Calabresi further embraces the concept of synergy between two drugs.

Applicants have canceled Claim 2. Claims 1 and 3 have been amended to recite the use of a compound of the general Formula II as recited with an antimetabolite antitumor substance chosen from 5-fluorouracil, fludarabin, gemcitabin and cytarabin. Applicants note that none of pending Claims 1 or 3 as amended encompasses the use of miltefosine, cisplatin, oxaliplatin, or carboplatin as taught by Hilgard. Neither Hilgard nor Calabresi teaches the use of compounds of Formula II as recited in Claims 1 or 3 for the treatment of mammary carcinoma. Accordingly, the cited references do not teach all of the elements of Claims 1 and 3.

Moreover, as taught by Principe et al. *Anti-Cancer Drugs* (1992), 3, 577-587 (“Principe;” already of record) whether a synergistic result is obtained depends on both the cell type and on the specific agents used. In the second paragraph on page 581 of Principe, the authors teach that in A427 cells, supra-additive effect is observed with the combination of ether phospholipid ET-18-OCH<sub>3</sub> and ADM, CDDP, or BLM. However, in the same cell line (*i.e.*, A427 cells), a sub-additive effect is observed with the combination of ether phospholipid ET-18-OCH<sub>3</sub> and VLB or VP-16. The fact that a particular compound has shown activity in a particular cell type (*e.g.*, mammary carcinoma) does not mean that a combination of that same compound with another antitumor agent will be effective in that same cell type (*i.e.*, the combination could be sub-additive). One cannot reliably predict how a particular cell type will react to a particular combination of agents. Therefore, the use of miltefosine in combination with a platinum based chemotherapeutic agent (as disclosed by Hilgard) would not render obvious to a person of ordinary skill in the art the use of a compound that is not miltefosine in combination with a compound that is not a platinum based chemotherapeutic agent. Accordingly, Applicants respectfully traverse the rejection of Claims 1 and 3 as amended over Hilgard in view of Calabresi.

Moreover, as the declaration of Dr. Guenther demonstrates, the combination of perifosine with particular antimetabolite antitumor substances produces a useful synergistic effect against breast cancer that could not have been predicted in view of teachings of the cited references. In his declaration, Dr. Guenther uses the combination index (CI) to show the synergism between perifosine and each of gemcitabin and cytarabin (*see* Table 3). As described in paragraph 9 thereof, the CI method, developed by Chou and Talaly in 1984, is one of the most popular methods to evaluate drug-drug interactions and to quantitatively depict synergism. Not only does the data in Table 3 clearly demonstrate that perifosine in combination with the listed antimetabolite antitumor agents, gemcitabin and cytarabin, produce a useful synergistic effect against breast cancer, but that the synergistic effect is advantageously greater at lower concentrations, which are more relevant in the treatment of humans. These results are unexpected because one can not foresee which combination of perifosine is useful (synergistic) and which combination is not useful (antagonistic) in a specific cancer entity, based on the activity of individual antimetabolites shown in Table 2 or on the teachings of the prior art.

Accordingly, Applicants respectfully traverse the rejection of Claims 1 and 3 over Hilgard in view of Calabresi.

**2.) Rejection of Claims 1-5 and 8-13 over Hilgard et al., Cancer Chemother. Pharmacol., (1993) 32: 90-95 (“Hilgard”) in view of Calabresi et al., Goodman & Gilman’s, The Pharmacological Basis of Therapeutics, Ninth Edition (“Calabresi”), in further view of Hilgard et al., Advances in Experimental Medicine and Biology, (1996) 157-164 (“Hilgard II”), and in further view of Principe et al. Anti-Cancer Drugs (1992), 3, 577-587 (“Principe”).**

Only Claims 1, 3, 4 and 12 remain in this application. Therefore, the rejection of Claims 2, 5, 8-11 and 13 is moot.

The Office action states, in essence, that one of ordinary skill in the art would have been motivated by the combination of Hilgard, Hilgard II, Calabresi and Principe to administer an adjuvant therapy of alkylphospholipids with other antineoplastic agents such as cisplatin because Hilgard, Hilgard II, and Principe teach the use of other antineoplastic agents with this class of drugs.

Claims 1, 3, 4, and 12 as amended, are directed to methods (claims 1, 3, and 4) and a drug product (claim 12) for treating mammary carcinoma by administering a compound of Formula II (*e.g.*, perifosine) in combination with an antimetabolite antitumor substance chosen from fluorouracil, fludarabin, gemcitabin and cytarabin. As discussed above, Principe et al. teaches that whether a synergistic result is obtained depends on both the cell type and on the specific agents used. One cannot reliably predict how a particular cell type will react to a particular combination of agents. Therefore, the use of, for example, perifosine in combination with a platinum based chemotherapeutic agent to treat mammary carcinoma (as disclosed by Hilgard II) cannot render obvious to a person of ordinary skill in the art the use of a compound that is not perifosine in combination with a compound that is not a platinum based chemotherapeutic agent.

Moreover, as the declaration of Dr. Guenther demonstrates, the combination of perifosine with particular antimetabolite antitumor substances produces a useful synergistic effect against breast cancer that could not have been predicted in view of teachings of the cited references. In particular, Dr. Guenther uses the combination index (CI) to show the synergism between perifosine and each of gemcitabin and cytarabin (*see* Table 3). As described in paragraph 9, the CI method, developed by Chou and Talaly in 1984, is one of the most popular methods to evaluate drug-drug interactions and to quantitatively depict synergism. Not only does the data in Table 3 clearly demonstrate that perifosine in combination with the listed antimetabolite antitumor agents, gemcitabin and cytarabin, produce a useful synergistic effect against breast cancer, but that the synergistic effect is advantageously greater at lower concentrations, which are more relevant in the treatment of humans. These results are unexpected because one can not foresee which combination of perifosine is useful (synergistic) and which combination is not useful (antagonistic) in a specific cancer entity, based on the activity of individual antimetabolites shown in Table 2 or on the teachings of the prior art.

Accordingly, Applicants respectfully traverse the rejection of Claims 1, 3, 4 and 12 as amended over Hilgard in view of Calabresi, in further view of Hilgard II, and in further view of Principe.

**3.) Rejection of Claims 2, 7, and 10 over Hilgard et al. Cancer Chemother. Pharmacol, (1993) 32:90-95 (“Hilgard”) in view of Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374 (“Stekar”).**

The Office action states that the combination of miltefosine with platinum based drugs as disclosed in Hilgard showed considerable synergy, and that a one of ordinary skill in the art would expect other platinum drugs to demonstrate similar synergy. The Office action also states that the combination of miltefosine with other antitumor agents would be obvious as a result of the combination of the teachings of Hilgard and Stekar.

Applicants have canceled Claims 2, 7 and 10.

## CONCLUSION

Based on the foregoing amendments and remarks, submitted along with an IDS, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case be passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

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Respectfully submitted,

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